PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

13 March 2023

Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) – Updated recommendations to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi).

Dear Healthcare Professional,

AbbVie, Galapagos, Lilly and Pfizer in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- **An increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality has been observed in patients with rheumatoid arthritis (RA) with certain risk factors using JAKi treatment compared to TNFα inhibitors.**
- **These risks are considered class effects and relevant across all approved indications of JAKi in inflammatory and dermatologic diseases.**
- **These JAKi should only be used if no suitable treatment alternatives are available in patients:**
    - **65 years of age and older;**
    - **who are current or past long-time smokers;**
    - **with other cardiovascular or malignancy risk factors.**
- **JAKi should be used with caution in patients with VTE risk factors other than those listed above.**
- **Dosing recommendations are revised for some patient groups with risk factors.**
- **Periodic skin examination is recommended for all patients.**
- **Prescribers should discuss with patients the risks associated with the use of JAKi.**

Background on the safety concern

The JAKi Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) are approved for the treatment of several chronic inflammatory disorders (rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, atopic dermatitis, and alopecia areata). The approved use differs for the different products, as outlined in the respective product information.

In March 2021, a Direct Healthcare Professional Communication (DHPC) for Xeljanz (tofacitinib)[1] was sent to healthcare professionals, informing them that data from a completed clinical trial (A3921133)[2] in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, suggest a higher risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor.

An additional DHPC[3] was sent in July 2021 to inform about an increased incidence of myocardial infarction, lung cancer, and lymphoma with tofacitinib compared to TNF-alpha inhibitors observed in the same clinical trial, as well as adopted recommendations for the product information of tofacitinib.

Preliminary findings from an observational study (B023) involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular events and VTE in patients with RA treated with Olumiant compared with those treated with TNF-alpha inhibitors.

Following the finalization of the review procedure of the available data across these five JAKi by EMA, recommendations have been adopted as specified in the "summary" above. The product information and the educational materials for healthcare professional and patients is being updated accordingly.

This letter is not intended as a complete description of the benefits and risks related to the use of these products. For further details, please refer to the updated SmPC for the respective products.

Please share this document with relevant members of your team.

Call for reporting

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system. Please find the relevant contact for each product in the table below.

[1] https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-initial-clinical-trial-results-increased-risk-major-adverse-cardiovascular

[2] Ytterberg, Steven R., et al. "Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis." *New England Journal of Medicine* 386.4 (2022): 316-326.

[3] https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-increased-risk-major-adverse-cardiovascular-events-malignancies-use-tofacitinib

Product	**Cibinqo (abrocitinib)**	**Jyseleca (filgotinib)**	**Olumiant (baricitinib)**	**Rinvoq (upadacitinib)**	**Xeljanz (tofacitinib)**
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Telephone number	1800 633 363	00800 7878 1345	01 664 0446	+353 1 428 7934	1800 633 363
Email address	medical.information@pfizer.com	DrugSafety.UK.Ireland@glpg.com	UKMedInfo@Lilly.com	IEPV@abbvie.com	medical.information@pfizer.com

Company contact point

Product	**Cibinqo (abrocitinib)**	**Jyseleca (filgotinib)**	**Olumiant (baricitinib)**	**Rinvoq (upadacitinib)**	**Xeljanz (tofacitinib)**
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Website address	www.pfizermedicalinformation.ie	www.glpg.com	UKMedInfo@Lilly.com	irelandmedinfo@abbvie.com	www.pfizermedicalinformation.ie
Postal address	Pfizer Healthcare Ireland, 9 Riverwalk, National Digital Park, Citywest Business Campus, Dublin 24, Ireland	Galapagos Biotech Ltd, Orega Uxbridge, Belmont, Belmont Road, Uxbridge UB8 1HE	Eli Lilly & Company Limited, Lilly House, Basing View, Basingstoke, Hampshire, RG21 4FA UNITED KINGDOM	AbbVie Medical Information Ireland, 14 Riverwalk, Citywest Business Campus, Dublin 24, D24 XN32, Ireland	Pfizer Healthcare Ireland, 9 Riverwalk, National Digital Park, Citywest Business Campus, Dublin 24, Ireland

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance website; www.hpra.ie.

Sincerely,

Caitriona McCarthy MPharm MPSI Senior Medical Manager Inflammation and Immunology Pfizer Healthcare Ireland	Mohammad Al-Addai Senior Medical Director UK & Ireland Galapagos Biotech Ltd, UK	Eddie Guzdar Senior Medical Director, Immunology Northern European Hub Eli Lilly & Company Limited, UK	Karine Egan Medical Director AbbVie Limited
DocuSigned by: Caitriona McCarthy 0490C1D2F7D4412...	DocuSigned by: Mohammad Al-Addai 522E45D5207C405...	DocuSigned by: Eddie Guzdar C4874392DF194F7...	DocuSigned by: Karine M Egan D7AEB439581B407...